REMARKS

I. Status of the Claims

Claims 29, 30, 32-39, 41, 43-51 and 58 are pending and stand rejected under 35 U.S.C. §103. The specific ground for rejection, and applicants' response thereto, are set out in detail below.

II. Objection

Claims 29 is objected to as claiming a non-elected embodiment. Applicants note that, to the extent the claim does in fact encompass *in vivo* aspects, it constitutes a linking claim and linking claim practice would apply (applicants entitled to examination of the linking claim at such point as the elected subject matter is found allowable; see MPEP §809). Thus, it is believed that the objection should be held in abeyance.

III. Rejections Under 35 U.S.C. §103

A. Hartley *et al.* and Christ & Dröge

Claims 29, 32-35, 41, 44, 45 and 58 stand rejected over Hartley *et al.* and Christ & Dröge. The examiner states that the skilled artisan would have modified the method taught by Hartley *et al.* by utilizing the mutant *lambda* integrases Int-h and Int-h/218 described in Christ & Dröge for their method of generating chimeric DNA. Applicants traverse.

In *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), the Federal Circuit took the Federal Circuit stated that in order for an examiner to make out a *prima facie* case of obviousness two things must be shown: (1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition; and (2) the prior art must have demonstrated a

reasonable expectation of success of the invention. The present rejection fails in both these regards.

As explained previously, Hartley *et al.* teach recombinational methods in prokaryotic and eukaryotic host cells using, *inter alia*, the lambda integrase recombination system. However, in contrast to the present invention that uses modified lambda integrases, Hartley *et al.* use exclusively the ***wild-type*** lambda integrase. In contrast, Christ & Dröge, like the present invention, use modified lambda integrases such as Int-h and Int-h/218, but this reference describes recombination performed in ***prokaryotes***, and as such does not give even the slightest hint that the described modified integrases could also promote recombination events in ***eukaryotic*** cells.

Furthermore, applicants have provided a number of particular concerns to support their position that one of skill in the art would not *a priori* find the combination of these references appropriate, much less to provide the requisite likelihood of success. For example, in the declaration of Dr. Dröge, it is stated that whereas the prokaryotic genome is circular and condensed due to negative supercoiling and architectural proteins like IHF, the eukaryotic genome is comprised of linear DNA molecules which are highly condensed in nucleosomes by histone proteins. The skilled artisan knows that lambda integrase-mediated recombination is highly dependent on the topological status of the DNA to be recombined and distinct accessory factors. In particular, integrase mediated recombination is dependent on distinct bending specificities of the DNA to allow the formation of DNA/protein complexes which finally give rise to the recombination event (see Christ & Dröge, p. 826, left col., 2nd para to right col. 2nd para).

Thus, without the aid of topologically underwound DNA, which exists only in prokaryotic cells, it was reasonable to assume that mutant Int proteins cannot function. The examiner has attempted to rebut this argument by stating that the claims do not require that the first DNA segment be integrated into the eukaryotic host cell chromosome. In response, applicants have provided an amendment introducing this recitation into claim 29.

The examiner next argues that "conditions required by a wild-type λ Integrase to mediate a sequence specific recombination event **in prokaryotic cells are even more stringent than those** required by the Int-h ..." (emphasis in original). However, the point made above is that the situation vis-à-vis topology is quite different in eukaryotic cells, and thus one cannot extrapolate from what is known about wild-type *versus* the modified Int-h in prokaryotes. Moreover, even considering the data of Lange-Gustafson that allegedly shows that Int-h works better with supercoiled DNA, applicants submit that the studies described in this paper were performed *in vitro* and reflect conditions (25°C and KCl at 25 mM) that have ***nothing*** to do with the environment inside a living eukaryotic cell. Again, if the examiner has countervailing evidence with his personal knowledge, applicants request that it be made of record. 37 CFR §1.104(d)(2); MPEP §2144.03. In the absence of such information, applicants submit that the expert declaration on record provides unrebutted evidence regarding unpredictability.

In summary, applicants submit that prokaryotic and eukaryotic DNA properties are fundamentally distinct, so much so that the skilled artisan would not seriously contemplate transferring the modified integrase recombination system of Christ & Dröge to a eukaryotic host organism/cell, and even if they were so motivated, there was no reasonable expectation of success in so doing. Moreover, the attempted reliance on Lange-Gustafson is misplaced given the highly artificial conditions under which the experiments reported therein were conducted.

Hence, a combination of the teachings of Christ & Dröge with Hartley *et al.* is not supported on the record, and would not provide a reasonable expectation of success even if so combined. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

B. Hartley *et al.*, Christ & Dröge and Crouzet *et al.*

Claims 36-39 and 49-51 stand rejected over Hartley *et al.* in view of Christ & Dröge, cite as above, and Crouzet *et al.*, cited for teaching expression of Int and Xis from additional DNA segments. The defects set forth above, with regarding to Hartely *et al.* and Christ & Dröge, apply with equal force here, and Crouzet *et al.* do nothing to remedy them. It is remains a fact that, given the difference between prokaryotic and eukaryotic cells, there is no reasonable basis for combing the work of the first two references, and further combining them with the latter, while maintaining a reasonable expectation of success. At best, the examiner has presented an "obvious to try" argument which that PTO's reviewing court has rejected as a proper basis for *prima facie* obviousness. *In re O'Farrell*, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Reconsideration and withdrawal of the rejection is therefore respectfully requested.

C. Crouzet *et al.* and Christ & Dröge

Claims 29, 30, 32, 33, 41, 44-48 and 48 are rejected over the combined disclosures of Crouzet *et al.* and Christ & Dröge. The examiner states that the skilled artisan would have modified the method taught by Crouzet *et al.* by utilizing the mutant *lambda* integrases Int-h and Int-h/218 described in Christ & Dröge for their method of generating chimeric DNA. Applicants traverse.

Just as with the rejection above based on Hartley *et al.*, applicants submit that the rejection here is flawed as well. This is, again, due to the simple fact that Crouzet *et al.* worked with wild-type integrases, and Christ & Dröge worked in prokaryotic systems. There was no motivation for combining these two very distinct systems, and even if there were, there was no likelihood of success that they would be compatible, *i.e.*, that the modified integrases of Christ & Dröge would function in a eukaryotic system.

Thus, for the reasons set forth above, reconsideration and withdrawal of this rejection also is respectfully requested.

D. Crouzet *et al.*, Christ & Dröge, and Capecchi *et al.*

Claims 29 and 43 are rejected over Crouzet *et al.*, Christ & Dröge and Capecchi *et al.* Applicants traverse.

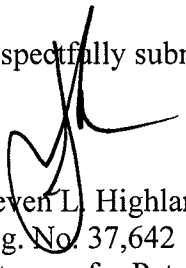
Just as with the previous rejections, applicants submit that the rejection here fails for lack of motivation and lack of an expectation of success. The defects of Crouzet *et al.* and Christ & Dröge have been discussed above and will not be repeated here. Capecchi *et al.*, which simply is cited for a "positive-negative selector vector," fails to address the issue of whether modified integrases would work in eukaryotic cells, as set out in detail above. Thus, again, there was no motivation for combining the primary and secondary references, and even if there were, there was no likelihood of success that they would work together.

Thus, for the reasons set forth above, reconsideration and withdrawal of this rejection also is respectfully requested.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to the effect is earnestly solicited. Should the examiner have any questions regarding the content of this response, a telephone call to the undersigned is invited.

Respectfully submitted,



Steven L. Highlander
Reg. No. 37,642
Attorney for Peter Dröge,
Nicole Christ and Elke Lorbach

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 536-3184

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